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博士学位论文

微囊藻毒素-LR在斑马鱼体内慢性毒性机制的研究

Toxicological study on the mechanism of chronic microcystin-LR toxicity in zebrafish (Danio rerio)

王明华

指导教师：王大志

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摘 要

微囊藻毒素-LR（缩写为MCLR）为水体中毒性最强、最经常爆发的一种毒素，该毒素对生物体呈多种毒性效应（如肝毒性和神经毒性），然而其毒性作用机制至今还不清楚。鉴于此，本研究工作以斑马鱼D. rerio为研究对象，进行不同低浓度MCLR（空白对照组、2和20 µg/L毒素处理组，暴露时间为30 d）慢性胁迫下鱼体内肝脏和大脑的蛋白质组学研究；即暴露30 d后，取斑马鱼的肝脏和大脑，采用双向凝胶电泳(Two-dimensional electrophoresis，简写为2-DE)和基质辅助电离解析飞行时间质谱(Matrix-assisted laser desorption/ionization time-of-flight/time-of-flight mass spectrometer，简写为MALDI-TOF/TOF-MS)等方法，研究MCLR胁迫下两种组织蛋白质表达图谱所发生的变化，找出发生显著变化的差异蛋白点，对其进行功能鉴定，继而揭示了由MCLR毒性引起的蛋白质组的变化；另外，本文测定了肝脏和大脑对MCLR的累积量及其蛋白磷酸酶(Protein phosphatase，简写为PP)的活性，同时也从超微结构水平来探讨MCLR所诱导的肝脏细胞损伤程度。该研究工作旨在探讨MCLR对鱼类的慢性毒害效应及其毒性机制，同时为可特异地指示MCs污染的生物标志物的筛选提供理论和实践依据。主要研究结果如下：

1、暴露结束后，毒素胁迫显著提高处理组斑马鱼肝脏内MCLR的累积量和PP活性，如空白对照组中没有检测到MCLR的含量，而2和20 µg/L毒素处理组的MCLR含量分别为0.031和0.039 µg/mg DW；同样地，相对于对照空白组，20 µg/L MCLR处理组的PP活性显著提高2倍。有趣的是，免疫印记实验表明肝脏内蛋白磷酸酶2A（缩写为PP2A）含量与MCLR处理浓度无相关性。MCLR胁迫引起肝脏细胞超微结构的显著损伤：相对于空白对照组，处理组肝脏细胞内粗内质网发生普遍的肿胀，伴随着网槽的扩张或空泡化；线粒体也发生肿胀，许多线粒体失去嵴；最为明显的是，处理组肝脏细胞有蜂窝状结构体的出现。蛋白质组学分析结果表明有22个蛋白质斑点在毒素胁迫下发生显著的变化；经过鉴定，这些蛋白质参与细胞骨架的组装、大分子的代谢、氧化胁迫和信号传导；因此，MCLR慢性肝毒性可引起细胞骨架组装和生物大分子代谢的失常，诱导氧化胁迫的出现，伴随着细胞内信

号传导的扰乱。另外，MCLR慢性肝毒性可能启动活性氧（缩写为ROS）途径，而不是PP途径，后者为该毒素急性毒害效应的主要机制。

2、暴露实验结束后，毒素胁迫显著提高斑马鱼大脑内MCLR含量和PP活性，如空白对照组中没有检测到MCLR的累积，而2和20 µg/L MCLR处理组的毒素含量分别为0.030和0.053 µg/mg DW；同样地，相对于对照空白组，20 µg/L MCLR处理组的PP活性显著提高1.3倍。蛋白质组学分析结果表明大脑内有30个蛋白质斑点在毒素胁迫下发生显著的变化；经过鉴定，这些蛋白质参与细胞骨架的组装、生物大分子的代谢、氧化胁迫、信号传导、以及其它功能（如转运、蛋白质降解、细胞凋亡和蛋白质翻译）。综上所述，MCLR的神经毒性可引起氧化胁迫、细胞骨架组装和大分子代谢的异常，以及伴随着信号传导和其它功能（如蛋白质的降解、细胞转运、细胞凋亡和蛋白质翻译）的紊乱，暗示该毒素对斑马鱼大脑神经毒性的复杂性和多样性。斑马鱼大脑的PP活性随着MCLR浓度的增加而升高，可能与毒素胁迫下PP2C2的诱导表达相关。另外，该研究提示MCLR的慢性神经毒性启动于ROS和PP途径，然而PP途径与PP2C2的显著上调相关的。最后，MCLR可能具有内分泌干扰物质的效应，因为该毒素胁迫显著地诱导卵黄蛋白原的形成；然而具体原因和机制的探讨有待于进一步研究。

值得一提的是，MCLR肝脏毒性和神经毒性引起的蛋白质组变化很相似，即两种毒性均显著影响了参与细胞代谢、骨架蛋白组装、氧化胁迫和信号传导的细胞过程，说明了MCLR的多种毒性效应在某种程度上呈一致性，虽然MCLR神经毒性还特异地影响了细胞转运、蛋白质降解、细胞凋亡和蛋白质翻译的生化过程；然而，即使MCLR两种毒性影响了相似的细胞过程（如细胞代谢、细胞骨架蛋白的组装、氧化胁迫和信号传导），具体参与的蛋白质却不相同，暗示该毒素肝毒性和神经毒性的毒害效应可能存在不同的生化机制。总之，本研究清楚地展现蛋白质组学技术可有效地对MCLR在斑马鱼体内肝毒性和神经毒性的毒害效应进行一些机制上的探讨。

关键词：蛋白磷酸酶；蛋白质组学；肝毒性；活性氧；MCLR；神经毒性

Abstract

Microcystin-LR (MCLR) is the most toxic and most frequently encountered toxin in the aquatic environment. MCLR presents multi-toxicity (e.g. hepatotoxicity and neurotoxicity), however the exact mechanism of which is still unknown. So, this study investigated the protein profiles of zebrafish (Danio rerio) liver or brain chronically exposed to MCLR concentrations (2 or 20 µg/L) using the proteomic approach. Namely, after 30 d MCLR exposure, under the cooperation of two-dimensional electrophoresis (2-DE) and matrix-assisted laser desorption/ionization time-of-flight/time-of-flight mass spectrometer (MALDI-TOF/TOF-MS) analysis, this work examined the differential protein profiles of both the tissues (liver or brain), revealed the differential protein spots, and subsequently submitted them to MS identity, with being aimed at elucidating the proteomic change caused by MCLR toxicity. Also, this work investigated toxin accumulation and protein phosphatase (PP) activity in both the tissues under different MCLR treatments. Meanwhile, this study especially analyzedthe MCLR-induced damage in the hepatocytes at the ultrastructural level. Taken together, this work provides a new insight into MCLR toxicity and its toxic mechanism in fish, and helps to select out a potential biomarker for biomonitoring MCs pollution in the aquatic environment. The results of the present study are described as follows:

1. MCLR treatment significantly enhanced toxin accumulation and PP activity in in the treated zebrafish livers at the end of this exposure experiment. For example, no MCLR was detected in MCLR non-exposed zebrafish livers, while the toxin contents attained to 0.031 and 0.039 µg/mg DW, respectively, in the zebrafish livers exposed to 2 and 20 µg/L MCLR. Similarly, in comparison to the control, the hepatic PP activity increased two times in zebrafish livers exposed to 20 µg/L MCLR. However, using the antibody representing

a specific interaction with PP2A, the Western blot analysis indicated that the hepatic PP2A amount was independent of the ambient MCLR concentrations. MCLR caused a noticeable damage to liver ultrastructure, a widespread swelling in the rough endoplasmatic reticulum and mitochondria was observed in the MCLR-exposed hepatocytes, and a honeycomb-like structure was formed in the treated nucleoli. The proteomic analysis revealed that the abundance of 22 protein spots, measured by 2-DE, was remarkably altered in response to toxin exposure. These proteins were involved in cytoskeleton assembly, macromolecule metabolism, oxidative stress and signal transduction. Thus, the chronic effects of MCLR hepatotoxicity caused dysfunction of cytoskeleton assembly and macromolecule metabolism, and induced oxidative stress with a concomitant interference with cell signal transduction. We speculate that the chronic effects of MCLR hepatotoxicity might initiate the ROS pathway, instead of the PP pathway which is the main mechanism for MCLR acute toxicity.

2. MCLR treatment obviously enhanced toxin accumulation and PP activity in the treated zebrafish brains after the 30 d exposure. For instance, no MCLR was detected in the control while the toxin contents were 0.030 and 0.053 µg/mg DW in the brains exposed to 2 and 20 µg/L MCLR. Similarly, compared to the control, the brain PP activity increased 1.3 times in zebrafish brains exposed to 20 µg/L MCLR. The proteomic analysis indicated that the abundance of 30 protein spots was remarkably altered in response to MCLR exposure. These proteins are involved in cytoskeleton assembly, macromolecule metabolism, oxidative stress, signal transduction, and other functions (e.g. transporting, protein degradation, apoptosis and translation). Overall, MCLR neurotoxicity induced oxidative stress, and a dysfunction of cytoskeleton assembly and macromolecule metabolism, with a concomitant interference with signal transduction and other functions (e.g. protein degradation, transport, apoptosis and translation), suggesting that MCLR toxicity to the zebrafish brain

was complex and diverse. Also, the PP activity in the brain was enhanced with an increasing MCLR concentration, and this was partly exemplified by an overexpression of PP2C2 under toxin treatment. Thus, our study firstly demonstrated that the chronic neurotoxicity of MCLR might initiate the PP pathway via an upregulation of PP2C in the zebrafish brain, in addition to the ROS pathway. Interestingly, an increased vitellogenin expression in the treated group suggested that MCLR might mimic the effects of endocrine disruption compounds, and this really deserves further study.

It should be noted that the responses in brain were quite similar with liver in our study, i.e. both toxicities exerted a significant effect on the similar cellular processes overlapped in general functional categories (e.g. metabolism, cytoskeletonal assembly, oxidative stress and signal transduction), highlighting that to some extent, there is a similarity in MCLR multi-toxicities, although MCLR neurotoxicity specifically affected transport, protein degradation, apoptosis and translation in zebrafish brains. However, even though the affected cellular processes were overlapped in general functional categories (e.g. metabolism, cytoskeletonal assembly, oxidative stress and signal transduction), none of the proteins in the functional category in brain was the same as that from liver., and a different biochemical mechanism might be involved in the intitiation of these two toxicities. Taken together, proteomics provides a potential tool for studying the biochemical mechanisms concerning MCLR toxicity in zebrafish.

Keywords: Protein phosphastase; Proteomics; Hepatotoxicity; Reactive oxygen species; MCLR; Neurotoxicity

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